"Keep up the good work!": A case study of the effects of a specific cognitive training in Alzheimer's disease.

ORIGINAL ARTICLE

“Keep up the good work!”: A case study of the effects of a specific cognitive training in Alzheimer’s disease

RUNNING TITLE:

Cognitive training in Alzheimer’s disease

Abstract

Alzheimer's disease (AD) is a neurodegenerative condition characterised by significant impairment in multiple cognitive domains. In recent years, the development of cognitive training in AD has received significant attention. In the present case study we designed a cognitive training **program** (GEO, Geographical Exercises for cognitive Optimization) based on an errorless paradigm and tailored to the patient's cultural interests. The aim of this training was to investigate the potential for acquiring and possibly retaining both procedural and verbal knowledge in early-stage AD. This study involved an 80-year old female patient diagnosed with early-stage AD, and 10 matched healthy subjects. Participants were asked to perform the two GEO training tasks: a 'puzzle-like' task for procedural memory, and an 'association' task for verbal memory. Both the patient and the healthy controls were subsequently trained with GEO using the same two tasks for two months. Although the patient's performance before training in both tasks was poor compared to healthy controls, after the training these differences disappeared. Our results showed that the patient was able to acquire new procedural abilities and verbal knowledge, and that her achievements were stable at **the follow-up testing scheduled three months after the end of the intervention**. This case study suggests a potentially useful strategy for cognitive training in AD.

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Introduction

Alzheimer's disease (AD) is the most common form of dementia, and its clinical manifestation includes significant memory deficits, as well as other cognitive deficits such as aphasia, apraxia and/or agnosia, that significantly interfere with everyday life (McKhann et al., 1984; Harciarek & Jodzio, 2005). AD typically affects the patient, their family and their social network through its deep impact at neural, psychological and social levels (Cheston & Bender, 1999). Cognitive training in patients with AD has been considered unsuccessful for a long time. About 15 years ago, it was claimed that cognitive training appeared to achieve almost negligible, short-term improvements in cognitive functioning, which were not sustained after the end of the training sessions (Rabins, 1996). A consensus statement on interventions for patients with AD corroborated this view, finding limited benefit in psychological approaches (Small et al., 1997).

The perception that cognitive training has limited usefulness in patients with AD has changed over the last few years. Specifically, new evidence has shown that cognitive training can allow patients with AD to reinforce individual cognitive abilities, specifically executive functions and procedural memory (van Halteren-van Tilborg, Scherder, & Hulstijn, 2007; Farina et al., 2002). However, caution is warranted due to the methodological limitations that characterize some of these studies, including small sample sizes and ambiguous terminology (Clare & Woods, 2004).

The application of cognitive training in AD is based on a rationale derived from evidence regarding the neuropsychology and neuroanatomy of memory impairments in AD and the capacity of the patients with AD to acquire new knowledge (Clare, 1999; Clare, Wilson, Carter, Hodges, & Adams, 2001). Converging evidence indicates that some cognitive subsystems (e.g. procedural memory) remain relatively intact, whilst others (e.g., episodic memory) are severely impaired

(Brandt & Rich, 1995; Salmon & Bondi, 2009). These dissociations are indeed supported also by a developing understanding of the role played by different brain areas in the cognitive processes of memory encoding, storing and retrieval. The brain areas most affected in the early stages of AD are mainly the medial temporal lobe structures, notably the transentorhinal region and the hippocampal complex, which are critical in the consolidation of new episodic memories (Glisky, 1998; Graham & Hodges, 1997; Nadel & Moscovitch, 1997). However, consolidation of semantic memories is not thought to rely heavily on the hippocampus (Kitchener, Hodges, & McCarthy, 1998; Vargha-Khadem et al., 1997). Therefore, while medial temporal lobe pathology is linked to the failure to rapidly encode new semantic information, other brain structures are involved in the integration of new information with existing knowledge during repeated cognitive training (Glisky, 1998; Kitchener, Hodges, & McCarthy, 1998).

Errorless learning is increasingly being recognised as a potentially useful paradigm to train memory in patients with mild to moderate AD (Baddeley & Wilson, 1994). This procedure aims to reduce errors to a minimum during learning in order to facilitate the acquirement of correct information. **For example, the association between the initial letters of a word and the word itself (e.g., a 5-letter word beginning with QU and the word "QUOTE") or between names of people and their corresponding faces, can be reinforced by making the association explicit and by asking the patient to re-state the association itself.** This is in contrast to trial-and-error learning paradigms, in which participants are encouraged to guess and consequently generate errors during learning. **In fact, Baddeley and Wilson (1994) suggested that patients who do not remember that an error was due to an incorrect response tend to repeat the same error because of recent activation in implicit memory. Thus, errors during encoding are more likely to be perpetuated, whereas preventing errors will support the patients in learning the right piece of information.**

In a systematic review of the literature, Grandmaison and Simard (2003) concluded that the errorless learning technique, which supports the encoding of new material, was a promising

paradigm for training memory in AD. The superiority of the errorless technique over the trial-and-error technique was also demonstrated by Metzler-Baddeley and Snowden (2005) on tasks involving both learning of new information and re-learning of material that was already familiar to the patients, a conclusion shared by a more recent literature review (Bier, Desrosiers, & Gagnon, 2006). In addition, in some cases it has been shown that improvements in the trained cognitive abilities were relatively stable at long-term follow-up (Clare, Wilson, Breen, & Hodges, 1999; Clare et al., 2000) and supported the re-learning of activities of daily living (Provencher, Bier, Audet, & Gagnon, 2008; Thivierge, Simard, Jean, & Grandmaison, 2008), although other studies have failed to consistently replicate these findings (Farina et al., 2002, Grönhoml-Nyman, Rinne, & Laine, 2010).

When planning cognitive training, researchers and clinicians focus on two key aspects: its *importance* for the patient (does the training make any sense for the patient?), and its *stability* (are the results relatively stable over time?). In the present case study we investigated the efficacy of a specific cognitive training in reinforcing a patient's verbal and procedural memory. The training implemented, based on the errorless paradigm, was tailored to the patient's interests (i.e. it was *important* to the patient) **and included a follow-up session three months after the end of the training** to test whether the results were *stable*. We aimed to assess whether it was possible to significantly reinforce the cognitive abilities targeted through this training, despite the progression of the degenerative disorder.

Materials and Methods

Participants: The present study involved one patient with early-stage AD and ten healthy controls.

The patient (C.O.) was an 80 year old female with 8 years of formal education. She was referred to the Assisted Health Residence "Ville Roddolo" (Moncalieri, Italy) for progressing memory problems, which started less than one year before and resulted in dangerous behaviours (e.g., she forgot to close the gas tap a few times after cooking, and she tended to lose her papers and keys frequently). At the time of referral, C.O. had been living on her own for ten years following her husband's death. Six months before the beginning of the present study, a comprehensive clinical assessment, including two consecutive brain MRI scans, was arranged by Consultant Neurologists, who made a diagnosis of early-stage probable AD, according to standard NINCDS-ADRDA diagnostic criteria (McKhann et al., 1984). Immediately after the diagnosis, C.O. commenced pharmacotherapy with an acetylcholinesterase inhibitor (donepezil). C.O. did not have any significant general health co-morbidities (e.g., diabetes or hypertension) at the time of this study.

With regards to the control group, 20 potential participants recruited from the same Assisted Health Residence were carefully screened in order to identify persons with no significant health problems such as cognitive impairment, diabetes, hypertension and neuropsychiatric disorders. At the end of the screening stage, 10 healthy controls (eight females, mean age 80.6 ± 3.4 years, range 78-85 years, mean years of formal education 8.6 ± 2.5) participated in the study. All of them were living in the Assisted Health Residence "Ville Roddolo" as they were widows with no children or other significant family members, and due to their advanced age they preferred leaving their own houses and sharing an assisted living environment. **In order to exclude from the control group participants with possible cognitive impairment, we only included subjects with a MMSE score > 26 (mean 28.7, SD 1.2, range 27-30) and with no history of psychological or medical conditions known to be associated with cognitive problems.**

Through a careful analysis of their clinical records and a detailed clinical interview (based on Green, 2000), we were able to exclude the presence of past or current substance abuse. In addition, none of the healthy controls were related to the patient involved in the study.

The study was granted approval by the local Research Ethics Committee. Informed written consent was obtained from all participants, and from the patient's caregivers.

Neuropsychological assessment: All participants underwent a detailed neuropsychological assessment by an experienced neuropsychologist (M.C.), in order to obtain detailed information about their performance across a wide range of cognitive domains. Specifically, the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975) and the Short Intelligence Test (Test di Intelligenza Breve, T.I.B., Colombo, Sartori, & Brivio, 2002) were administered, as a screening measure for cognitive impairment and a measure of premorbid Intelligence Quotient, respectively. Memory was assessed by administering digit span forwards and backwards (Wechsler, 1987), the two-syllable words repetition test (Spinnler & Tognoni, 1987), and the Rivermead Behavioural Memory Test (RBMT, Wilson, Cockburn, & Baddeley, 1985). Semantic knowledge was assessed by the Graded Naming test (McKenna & Warrington, 1983). Language was assessed by the Token test (De Renzi & Vignolo, 1962). Visuospatial abilities were assessed using three subtests of the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991): object decision, position discrimination, and number location. Executive tasks included both timed and untimed tests. Timed tests encompassed letter (F, A, S) and category (animals) spoken verbal fluency tasks (Novelli et al., 1986), as well as the Hayling Sentence Completion test (Burgess & Shallice, 1997). As an untimed executive test, participants were administered the Brixton test (Burgess & Shallice, 1997).

Neuropsychiatric assessment. Emotional disturbances were investigated by administering the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983), a brief self-assessment scale that provides a valid and reliable measure of severity of anxiety and depression.

Cognitive training (GEO, Geographical Exercises for cognitive Optimization): Since the first assessments at "Ville Roddolo", C.O. displayed a strong interest for geography. Although she did not get any formal education in geography during her life, reading books and watching television programs about journeys and other geographical issues clearly emerged as her main hobby. Given C.O.'s significant interest in geography, we decided to use geographical materials for the cognitive training. More precisely, we designed a simplified model of the world that required subjects to arrange 16 countries in their right place **in the model** in the shortest possible time, in a 'puzzle-like' fashion ('puzzle-like' task). **Examples of countries included United States of America, South-Africa, and Great Britain**. The 16 wooden pieces (each representing one country) varied in dimensions and colours, **but showed the shape of the countries they represent**. A fixed order of the pieces was set up in front of the participant every time (see Figure 1). **To ensure that the order of the pieces did not vary across trials and subjects, the border of each piece was marked by a coloured pen on the model, so that the experimenter could quickly locate each piece always to the same place in front of the subject.** Participants were invited to start from the easier pieces (e.g., the bigger ones), in order to complete the whole task quickly. They were asked not to guess, so the procedure was entirely error-free.

FIGURE 1 ABOUT HERE

In order to train and test the association with verbal material ('association' task) too, we identified a city for each of the countries involved: we opted for easy-to-pronounce cities. **Examples of cities include 'Aurora' for USA, 'Albertinia' for South-Africa, 'Bath' for Great Britain.** At the beginning of the training session and thus before the completion of the 'puzzle-like' task, the list of cities associated to their **corresponding** countries was read to the subject three times, with a slow rhythm of a name every four seconds, after which the participant was invited to repeat each association between country and city names, to facilitate the learning procedure **of the correct association**. After the completion of the 'puzzle-like' task, the examiner said aloud the name of a country, and the participants **were asked to say** aloud the name of the associated city. Again, the participants were asked not to guess; if unsure, they were invited to say that they did not know the association of names, so the procedure was error-free. **To ensure real learning of meaningful associations, rather than learning of a sequential list of pairs, the sequence of the countries presented to the participant to elicit the corresponding name of the city changed randomly on each trial.**

These two tasks ('puzzle-like' and 'association' tasks) made up the cognitive training used throughout the study (GEO). Each participant underwent the 'puzzle-like' task and the 'association' task at the beginning of the study (T_0), and both the time of completion (for the 'puzzle-like' task) and the number of cities correctly associated with countries (for the 'association' task) were recorded. Regarding the 'puzzle-like' task, lower scores (i.e. completion time in seconds) represent better performance, whereas for the 'association' task higher scores (i.e. number of correct associations between cities and countries) represent better performance. During training, each participant underwent a session of practice with GEO three times a week for a month.

After one month of training, participants' performance was recorded again (T_1). Then, the cognitive training continued under the same conditions for another month, with another testing session at the end (T_2). **The training was discontinued after T_2. Lastly, a follow-up session was scheduled three months after the end of the training (T_3)**. At T_1, T_2 and T_3 the MMSE was administered to all

participants, in order to monitor their cognitive functioning over time. The assessment sessions for each participant at each testing point (T_0, T_1, T_2 and T_3) were video-recorded. Two experienced nurses, not involved in the design of the study and blind to the purposes of it, examined the recorded sessions in order to identify and register both the time of completion (for the 'puzzle-like' task) and the number of cities correctly reported by the participants (for the 'association' task). The inter-rater agreement between the two raters was high (Cohen's K = 0.88): the disagreement about four scores was resolved by discussion. To keep track of participants' awareness about the proposed tasks, at the beginning of each training session participants were asked to answer the following question: "Have you ever done this task before?". Then, the verbal instructions given to the participant were: "You can see in front of you a simplified model of the world. You can see a number of pieces that represent countries as well, and your job is to locate these pieces in the right place in the model of the world. Try to do the task *as soon as* you can". At the end of the task, the examiner always said: "Well done. Now, I want you to try and say the names of the cities associated with these countries. We went through these names a few minutes ago. Feel free to start from the city you want, and please say only the names you are pretty sure of. Keep up the good work!".

Descriptive statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 18.0. Comparisons of the patient's scores with healthy controls' scores were performed by means of modified *t*-tests, according to the procedure formalized by Crawford, Howell and Garthwaite (1998) and Crawford and Garthwaite (2002) to deal with single cases in cognitive neuropsychology. Firstly, C.O.'s scores on the neuropsychological and neuropsychiatric measures were compared to the scores of healthy controls. Secondly, in order to show the longitudinal effect of the GEO training, the difference between C.O.'s initial and final performances (T_3 - T_0)/ T_0) was compared with the corresponding difference in the healthy control group. Thirdly, C.O.'s performance on both the 'puzzle-like' and the 'association' tasks at each assessment (i.e. T_0, T_1, T_2 and T_3) was compared to the initial performance (i.e. T_0) of the healthy controls, in order to ascertain whether the patient's performance during the course of the training could reach the healthy

controls' baseline performance. Lastly, C.O's performance at each assessment was also compared to the healthy controls' performance at each intermediate assessment (i.e. patient's performance at T_1 and controls' performance at T_1, patient's performance at T_2 and controls' performance at T_2, and so on), in order to ascertain whether the patient's performance significantly differed from that of healthy controls' during the course of the GEO training.

Results

Neuropsychological assessment. C.O.'s scores were significantly worse than healthy controls' scores on the following tests: MMSE ($t(10) = 2.955$, $p = 0.016$), two-syllable words repetition test ($t(10) = 1.866$, $p = 0.047$); RBMT – standardized profile score ($t(10) = 7.812$, $p = 0.0001$); RBMT – story immediate ($t(10) = 5.864$, $p = 0.0001$); RBMT – story delayed ($t(10) = 7.847$, $p = 0.0001$); verbal fluency – letters ($t(10) = 3.042$, $p = 0.007$); and Brixton test ($t(10) = 2.293$, $p = 0.024$). In all of the other neuropsychological measures administered, C.O.'s performance did not differ significantly from healthy controls' performance. Participants' scores as well as the statistical comparisons of interest are shown in Table 1.

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TABLE 1 ABOUT HERE

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Neuropsychiatric assessment: The comparison of C.O.'s and healthy controls' scores on the HADS did not show the presence of any clinically or statistically significant differences (*anxiety:* C.O.'s score = 3, healthy controls' score = 3.50 ± 1.25, borderline range: 8-10, t(10) = 0.951, NS; *depression:* C.O.'s score = 4, healthy controls' score = 3.75 ± 1.49, borderline range: 8-10, t(10) = 0.875, NS).

Geography tasks: In order to investigate the presence of a longitudinal effect in C.O.'s performance, we first calculated the difference between the initial and final performances as $(T_3 - T_0)/T_0$, and then we statistically compared C.O.'s and healthy controls' differences by means of the modified *t*-test ('puzzle-like' task: C.O. = -0.42, healthy controls: -0.28 ± 0.04, t(10) = 3.337, p = 0.009; 'association' task: C.O. = 4.00, healthy controls: 0.25 ± 0.11, t(10) = 32.504, p < 0.001).

C.O.'s performance on the 'puzzle-like' task was subsequently compared to healthy controls' performance in two ways: 1) by comparing her performance at T_0, T_1, T_2 and T_3 with healthy controls' performance at T_0 (baseline), in order to test whether the cognitive training could allow C.O.'s performance to reach at least the baseline level; and 2) by comparing her performance at T_0, T_1, T_2 and T_3 with the corresponding controls' performance at T_0, T_1, T_2 and T_3, in order to test whether the training could allow C.O.'s performance to reach the level of healthy controls. C.O.'s performance on the 'association' task was compared with healthy controls' performance in the same way.

Regarding the 'puzzle-like' task, C.O.'s performance was significantly worse than baseline at T_0 only (t(10) = 2.510, p = 0.04). At the following assessments (i.e. T_1, T_2 and T_3), her performance did not differ significantly from baseline (T_1: t(10) = 0.472, p = 0.66; T_2: t(10) = 0.573, p = 0.60; T_3: t(10) = 0.03, p = 0.98). Then, C.O.'s performance at the four scheduled assessments (i.e. T_0, T_1, T_2 and T_3) was compared with the corresponding healthy controls' performance: again, C.O.'s performance significantly differed from that of healthy controls' at T_0 only (T_0: t(10) = 2.510, p =

0.04; T_1: t(10) = 1.704, p = 0.14; T_2: t(10) = 1.615, p = 0.16; T_3: t(10) = 1.647, p = 0.25). Table 2 (a) reports the comparisons of interest, and Figure 2 shows these results graphically.

TABLE 2 ABOUT HERE

FIGURE 2 ABOUT HERE

With regards to the 'association' task, C.O.'s performance at the four scheduled assessments was first compared to baseline: her performance was significantly worse than baseline at T_0 only (t(10) = 2.740, p = 0.02). Interestingly, at the following assessments (T_1, T_2 and T_3), C.O.'s performance did not differ significantly from **the baseline of the controls** (T_1: t(10) = 0.718, p = 0.51; T_2: t(10) = 1.863, p = 0.11; T_3: t(10) = 0.339, p = 0.76). C.O.'s performance was subsequently compared with the corresponding healthy controls' performance: again, her performance significantly differed from that of healthy controls' at T_0 only (T_0: t(10) = 2.740, p = 0.02; T_1: t(10) = 1.593, p = 0.16; T_2: t(10) = 0.304, p = 0.78; T_3: t(10) = 0.454, p = 0.68). Table 2 (b) reports the comparisons of interest, and Figure 3 shows these results graphically.

FIGURE 3 ABOUT HERE

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As previously mentioned, the MMSE was administered to all participants at each assessment (T_0, T_1, T_2 and T_3), in order to monitor their cognitive functioning over time. As expected, while healthy controls' performance was quite stable over time, C.O.'s performance showed a small decrease over time in absolute values (T_0: 25/30; T_3: 23/30), due to a poorer performance on the orientation items. Table 3 shows these results and the statistical comparisons of interest.

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TABLE 3 ABOUT HERE

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It is worth mentioning that when the question, "Have you ever done these tasks before?", was regularly asked to the participants at the beginning of each session, C.O. always replied "No", while all of the healthy controls always answered affirmatively after the first session of training.

Discussion

Cognitive training in AD has been considered of little utility for a long time. Only recently, a growing amount of evidence has started to challenge this traditional view, suggesting that patients undergoing structured cognitive training can show significant improvements as compared to untrained patients (Loewenstein, Acevedo, Czaja, & Duara, 2004; Clare & Jones, 2008). This raises the possibility that the implementation of specific rehabilitation training tailored to patients'

interests and preferences may actually be a fruitful way of supporting patients' abilities and limiting some aspects of their cognitive decline during the course of the disease.

In the present single-case study we implemented a cognitive training **program** based on the interest in geography in a patient with early-stage AD. The patient (C.O.) and 10 healthy controls recruited for this study were comparable in terms of both age and level of formal education. In addition, the comparison of C.O.'s and controls' performance on the neuropsychological measures administered showed that only a few measures reflected a significant difference in their performance. Specifically, C.O.'s performance was significantly worse than controls' performance only on the MMSE (**indicating the presence of a significant difference in her performance of a measure of general cognitive functioning**), the two-syllable words repetition test (**indicating the presence of a significant difference in her performance on a test of short-term verbal memory**), the RBMT (**indicating the presence of a significant difference in her performance on a test encompassing everyday memory problems**), the verbal fluency letters and the Brixton test (**indicating the presence of a significant difference in her performance on tests of executive functions**), **whilst the other measures did not show any significant difference between C.O.'s scores and the scores of healthy controls. We were thus confident that the patient was not cognitively too compromised to be involved in the cognitive training.** In order investigate the possibility that the cognitive performances were actually influenced by different levels of anxiety and depression, we ruled out the presence of significant differences between C.O. and healthy controls in terms of anxiety and depression, as measured by the HADS. Of note, the levels of anxiety and depression were well below clinical thresholds, allowing us to exclude the presence of significant anxiety or depression in our participants on both statistical and clinical grounds.

The GEO training encompassed two different tasks: the 'puzzle-like' task and the 'association' task. Although it is possible to assume that the first task also involved semantic knowledge (i.e. knowing were South Africa is may help the participant to locate the piece

representing South Africa more easily), from a qualitative point of view it is relevant to note that the participants' initial performance (i.e. T_0) was characterized by some errors, whereas during the training they followed the suggestion of starting from the easier pieces (i.e. the bigger ones) in order to avoid making errors. Thus, it can be reasonably assumed that the performance on this task relied more on procedural knowledge (i.e. learning where the pieces should be located correctly in order to perform the task more quickly in the following trials) than on semantic knowledge.

As far as the second task ('association' task) is concerned, we consistently invited the participants to verbalize only the associations of names they felt confident with, in order to minimize the effects of intrusions of errors, and reinforce the appropriate associations between the countries and the corresponding cities.

We found a significant longitudinal effect in C.O.'s performances across both tasks, compared to healthy controls' performance. More specifically, when the differences between final and initial performances were taken into account, we demonstrated that C.O.'s performance during the course of the study significantly improved across both tasks. This suggests that the learning of both new procedures and new verbal knowledge is still possible in patients with early-stage AD, and that these achievements can be maintained for at least three months after the end of the training.

Although at the beginning of the study C.O.'s performance was significantly poorer compared to the healthy controls, her performance on both tasks reached the baseline values of healthy controls after just one month of training. Interestingly, **she** exceeded in absolute values the baseline scores by the end of the scheduled two-month training. In addition, even though cross-sectional comparisons showed that C.O's scores were lower than that of healthy controls' in absolute values at both T_1 and T_2 training sessions, these differences were not statistically significant. C.O.'s performance showed a clear trend towards converging with that of healthy controls' over time, especially on the 'association' task.

It is interesting to note that both C.O. and healthy controls showed an improvement in their performance over time, even if a greater improvement was seen in C.O., as compared to controls. **Ceiling effect is crucial when dealing with experimental studies, especially when new tools are used. However, it is unlikely that the two tasks included in the GEO training were characterised by such an effect, at least in this pattern of results: in the 'puzzle-like' task there is theoretically always space for indefinite time performance improvements, and in the 'association task' only one out of the 10 healthy controls reached the maximum score of 16 at T2, whereas no one reached this score at the other assessment points.**

A possible explanation of the greater improvement seen in C.O. may be that a greater improvement can be expected in subjects that have some cognitive impairment at baseline, as they could fruitfully benefit of the training and gain a significant improvement in their performance. Conversely, the potential for improvement is likely to be lower in healthy controls, who are typically already good at baseline. However, future studies should specifically clarify this issue.

An important finding of the study came from participants' performance at the follow-up, scheduled three months after the end of the cognitive training (i.e. T_3). C.O.'s performance on both tasks showed significant stability, suggesting that the achievements she had made during the course of the cognitive training were maintained for at least three months after the end of the intervention. Her performance on both tasks was quite stable after the end of the training, even when it was compared to the corresponding performance of healthy controls (i.e. performances at T_3 were directly compared). Thus, the current study suggests that C.O. not only demonstrated the acquisition of both procedural abilities and verbal knowledge, but that she was also able to retain these achievements beyond the end of the rehabilitation training, similarly to healthy controls. **Interestingly, the stability in maintaining what she acquired during training was clear despite the possible cognitive decline during the course of the study, as suggested by the subtle decrease in absolute values of C.O.'s MMSE scores.**

The 'association' task was based on the errorless paradigm, which facilitates the encoding phase by reducing or eliminating errors in order to support the acquisition of the correct information (Baddeley & Wilson, 1994). Interestingly, C.O. was able to learn and retain for a relatively long time (at least three months) the newly acquired verbal information, showing that cognitive training tailored on patients' interests and based on errorless procedures can be helpful in supporting patients' learning as their neurodegenerative disease progresses.

At the beginning of the study, C.O. had been taking medication (i.e. donepezil) for six months, and she continued her pharmacotherapy throughout the cognitive training. However, since her cognitive deficits continued to increase during the pharmacological treatment alone (e.g., MMSE score decreased from 29 to 25 in a few months prior the beginning of the study), it is unlikely that medication *per se* could have played a significant role in driving C.O.'s achievements during the subsequent cognitive training.

A strength of the present study is that the performance of patient C.O. was compared to a small group of healthy controls via a series of modified *t*-tests specifically designed to deal with single case studies. This allowed us to directly compare C.O.'s performance with the performance of a control group recruited in the same setting and undergoing the same cognitive training. In addition, the two exercises proposed were tailored to C.O.'s interest for geography, and they only required a few minutes to be performed. Therefore, her high motivation and the short duration of training sessions (i.e. 30 minutes each) allowed us to implement an efficacious cognitive training that was not too demanding for her.

This study also has some limitations. Firstly, we did not assess C.O.'s awareness of her memory problems in a standardised way. We regularly asked each participant whether they had done the tasks at hand before, in order to have an indication of their general awareness, but a deeper investigation by means of specific measures (such as the Memory Awareness Rating Scale-Adjusted: Hardy, Oyebode, & Clare, 2006) could have provided a more rigorous assessment.

Secondly, we did not investigate the possible generalization of the capacities acquired during the training to similar cognitive tasks, in order to see whether these acquired abilities may be effectively applied to cognitive tasks other than the ones used during this training.

We believe that there is potential for this kind of intervention to be made available across different clinical settings, including Rehabilitation Centres, in consideration of the reduced costs in terms of materials and time. Moreover, therapists from different backgrounds could achieve familiarity with the administration procedure in one training session and the intervention itself is not unnecessarily time-consuming, thus representing a feasible and cost effective option for the consideration of health care managers and policy makers.

The present case study supports the view that when a patient's interests are taken into account, it is possible to successfully train at least some specific cognitive abilities. **However, a limitation of the present study is that the training intervention did not include a second task that was not in a specific area of the patient's interest. Future studies should focus on this relevant point, by comparing performances on tasks of interest versus 'neutral' tasks, in order to validate the generalizability of our findings.**

In our experimental paradigm, the patient was able to acquire and retain not only procedural abilities, but also explicit verbal knowledge, in keeping with previous studies suggesting the possibility of learning new verbal material by using an errorless paradigm. These findings should prompt further investigations in order to identify the degree of learning that patients affected by early-stage AD can achieve, and the degree of stability and generalizability of their newly acquired skills.

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	Patient C.O.	Healthy controls (n = 10)	Modified *t*-test

Wechsler, D. (1987). *Wechsler Memory Scale - Revised*. New York: The Psychological Corporation.

Wilson, B. A., Cockburn, J., & Baddeley A. (1985). *The Rivermead behavioural memory test manual*. Reading: Thames Valley Test Co.

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Age in years (SD)	80.0	80.6 (3.4)	-
Gender (M:F)	0:1	2:8	-
Education in years (SD)	8.0	8.7 (2.5)	-
MMSE	25	28.7 (1.2)	2.955 *
T.I.B. (Pre-morbid IQ)	116	118.4 (7.9)	NS
Digit span (forward)	6	7.8 (1.2)	NS
Digit span (backward)	5	6.6 (1.9)	NS
Two-syllable words repetition test	5	7.7 (1.4)	1.866 *
RBMT (standardized profile score)	9	18.3 (2.1)	7.812 **
RBMT (story immediate)	7	17.2 (1.7)	5.864 **
RBMT (story delayed)	3	14.4 (1.4)	7.847 **
GNT	24	27.5 (2.4)	NS

Token test	34	33.3 (1.2)	NS
VOSP (object decision)	19	19.1 (0.4)	NS
VOSP (position discrimination)	20	19.9 (0.1)	NS
VOSP (number location)	9	9.2 (1.2)	NS
Verbal fluency (letters)	35	44.7 (3.0)	3.042 **
Verbal fluency (category)	14	21.0 (4.5)	NS
Hayling test (overall score)	6	6.3 (1.3)	NS
Brixton test	4	7.8 (1.6)	2.293 *

Table 1. Demographic data and participants' baseline performance on general neuropsychological measures.

* $p < 0.05$; ** $p < 0.01$; IQ = Intelligence Quotient; GNT = Graded Naming Test; MMSE = Mini-Mental State Examination; NS = not significant; RBMT = Rivermead Behavioural Memory Test; SD = standard deviation; T.I.B. = Test di Intelligenza Breve (short intelligence test); VOSP = Visual Object and Space Perception battery.

Table 2. Results of the two geography tasks: (a) ‘Puzzle-like’ task; (b) ‘Association’ task.

Assessment	Patient C.O.	Healthy controls (n = 10)	Modified *t*-test

(a) ‘Puzzle-like’ task. Time of completion expressed as seconds (lower scores indicate better performance).

	vs HC T_0	315	180.60 (53.63)	2.510 *
T_0				
	vs HC T_0	315	180.60 (53.63)	2.510 *
	vs HC T_0	206	180.60 (53.63)	NS
T_1				
	vs HC T_1	206	129.00 (45.39)	NS
	vs HC T_0	140	180.60 (53.63)	NS
T_2				
	vs HC T_2	140	98.60 (25.75)	NS
	vs HC T_0	182	180.60 (53.63)	NS
T_3				
	vs HC T_3	182	129.85 (41.14)	NS

* $p < 0.05$; HC = healthy controls; NS = not significant; T_0 = assessment at the beginning of the study; T_1 = assessment after one month of training; T_2 = assessment at the end of the two-month training; T_3 = assessment at follow-up;

Assessment	Patient C.O.	Healthy controls (n = 10)	Modified *t*-test

	vs HC T_0	2	9.1 (2.6)	2.740 *
T_0				
	vs HC T_0	2	9.1 (2.6)	2.740 *
	vs HC T_0	11	9.1 (2.6)	NS
T_1				
	vs HC T_1	11	13.2 (1.4)	NS
	vs HC T_0	14	9.1 (2.6)	NS
T_2				
	vs HC T_2	14	14.6 (2.2)	NS
	vs HC T_0	10	9.1 (2.6)	NS
T_3				
	vs HC T_3	10	11.4 (3.1)	NS

(b) 'Association' task (higher scores indicate better performance, range 0-16).

* $p < 0.05$; HC = healthy controls; NS = not significant; T_0 = assessment at the beginning of the study; T_1 = assessment after one month of training; T_2 = assessment at the end of the two-month training; T_3 = assessment at follow-up;

Assessment	Patient C.O.	Healthy controls (n = 10)	Modified *t*-test

Table 3. Participants' MMSE scores at each assessment.

T_0	25	28.7 (1.2)	2.955 *
T_1	25	28.9 (1.1)	3.299 **
T_2	24	28.7 (1.0)	4.318 **
T_3	23	28.7 (1.2)	4.637 **

* $p < 0.05$; ** $p < 0.01$; T_0 = assessment at the beginning of the study; T_1 = assessment after one month of training; T_2 = assessment at the end of the two-month training; T_3 = assessment at follow-up;

Figure captions.

Figure 1. The geographical materials used.

Figure 2. C.O.'s performance on the 'puzzle-like' task versus baseline (a) and versus the corresponding healthy controls' performance (b). Scores are expressed as Z scores.

* p = 0.04

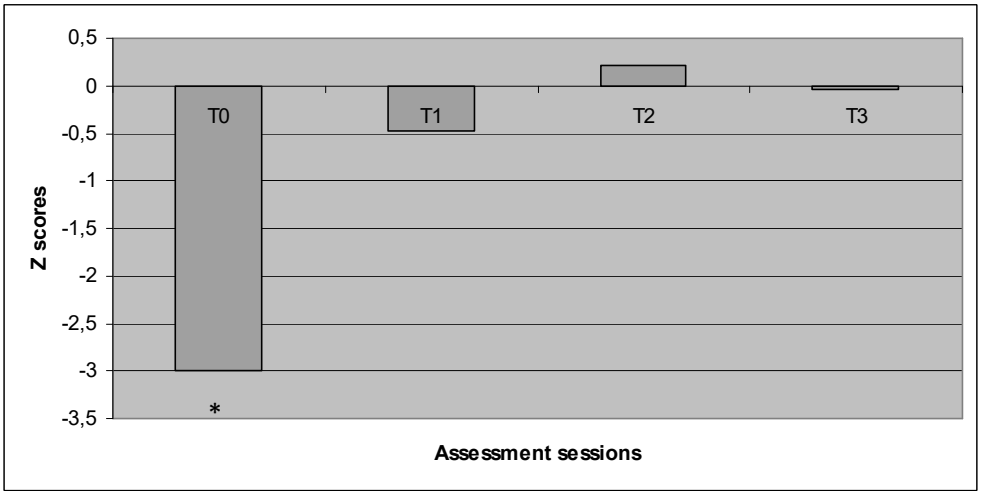
Figure 3. C.O.'s performance on the 'association' task versus baseline (a) and versus the corresponding healthy controls' performance (b). Scores are expressed as Z scores.

* p = 0.02

Figure 1.

Figure 2.

(a)



(b)

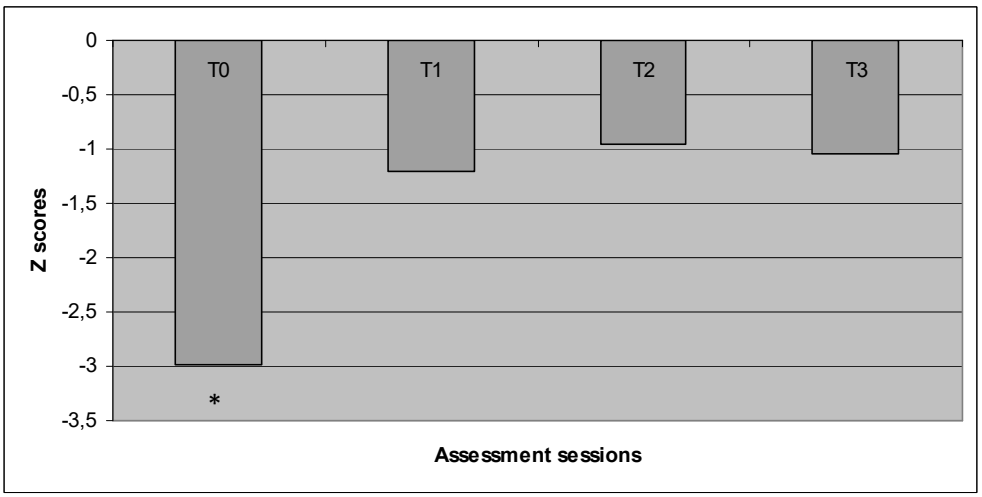
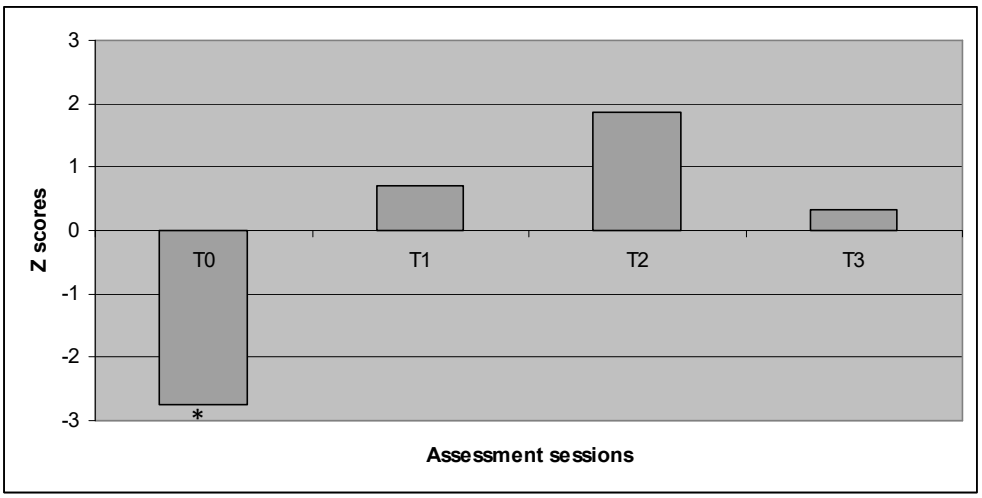
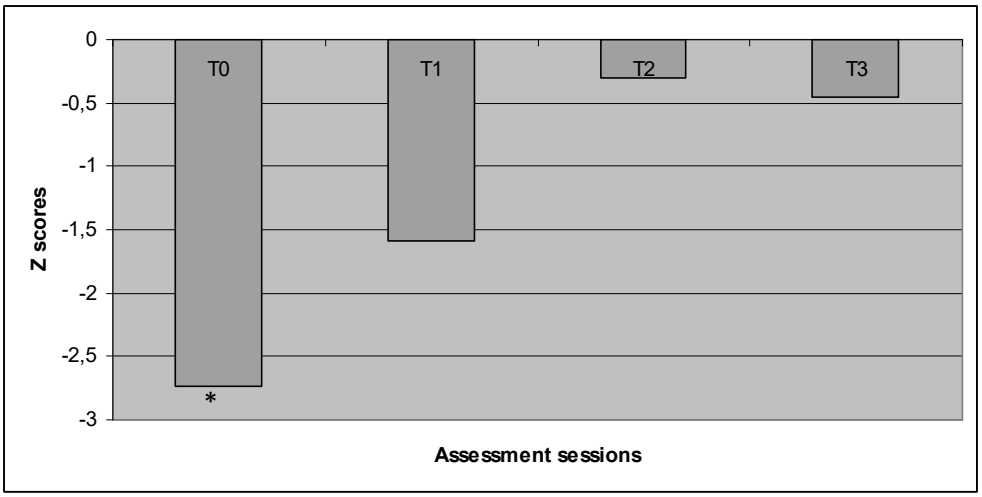


Figure 3.

(a)


3
2
1
0
-1
-2
-3
Z scores
T0
T1
T2
T3
*
Assessment sessions

(b)


0
-0,5
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-1,5
-2
-2,5
-3
Z scores
T0
T1
T2
T3
*
Assessment sessions